REMARKS

Claims 1-7 and 14-29 are presently pending. Claims 1, 3, 16 and 21 are amended to address the indefiniteness rejection discussed below. No new matter has been added herewith. The following addresses the substance of the Office Action.

Indefiniteness

Claims 1-7 and 14-29 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 1, 3, 16 and 21 recited the limitation wherein "a fraction of the thrombin has a specific activity of at least 2000 International Units per mg of protein". The Patent Office found that the phrase was indefinite because, while it required some fraction of the thrombin product to have a specific activity, it did not specify what fraction of the thrombin is required.

Applicants have amended Claims 1, 3, 16 and 21 to recite "wherein thrombin with a specific activity of at least 2000 International Units per mg of protein is generated". Accordingly, the claims, including dependent claims 2, 4-7, 14, 15, 17-20 and 22-29, are in compliance with the requirements of 35 U.S.C. § 112, second paragraph.

Obviousness

Kraus et al. in view of Piet et al. and Anderle et al.

Claims 1-6, 14, 16-19, 21-24 and 26-29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kraus et al. (U.S. Patent No. 5,143,838) in view of Piet et al. (1990 *Transfusion* **30**:591-598) and Anderle et al. (U.S. Patent Application publication No. 2003/0133829). Kraus et al. discloses conversion of prothrombin to thrombin on an anion exchange column. The Examiner acknowledges that Kraus et al. do not teach solvent-detergent inactivation on the anion exchange medium or sterilization of plasma prior to fractionation. However, the Examiner cited Piet et al., which allegedly teaches that sterilization methods can be applied at the time of plasma collection, prior to fractionation procedures. The Examiner concluded that Piet et al. was successful in obtaining thrombin fractions when sterilization was done prior to obtaining fractions. In particular, at page 8 of the Office Action, the Examiner cited Table 2 on page 595 of Piet et al. and asserted that Piet et al. were "successful with obtaining thrombin fractions with this order of steps".

The Applicant does not agree with the Examiner's interpretation of Piet et al., and believes that the Examiner's objections are misplaced. In contrast to the Examiners assertion, Table 2 of Piet et al. actually refers to factor II (prothrombin) and not thrombin. Moreover, Piet et al. does not discuss the activation of thrombin from prothrombin and the results of Piet et al., either alone or in combination with the other cited art, do not teach against the previously presented evidence that thrombin can not be activated from prothrombin after solvent-detergent virus inactivation of prothrombin. For example, Anderle et al. teaches that prothrombin is deactivated by conventional solvent-detergent methods.

More generally, Piet et al. relates to the detection of native proteins in the plasma (factors VIII, II, V, VII, IX & X, antithrombin III, albumin and immunoglobulins). Only limited tests were performed on the fractionated products, and only factor IX was measured as an indicator of fractionated prothrombin complex concentrate, PCC (Piet et al. page 593, right column penultimate paragraph, citing Table 3). Thus, the results for PCC shown in Table 3 describe only factor IX and do not claim the recovery of factor X or prothrombin, let alone the potential to generate thrombin from prothrombin. The proteins described by Piet et al. are all native plasma protein zymogens. Thrombin, which must be activated from prothrombin (factor II) zymogen, is not described.

Moreover, Piet et al. indicates that the yield of PCC from combined solvent/detergent-treatment plasma was lower than the untreated control clearly described for TNBP and Tween 80 (Piet et al. page 594, sentence bridging left and right columns) but also shown to a lesser extent for TNBP and Triton X45 (Piet et al. Table 3). Furthermore, on page 596, Piet et al. states that the use of TNBP alone eliminates questions related to the toxicology of added detergent; however, the effective elimination of virus with TNBP alone required a temperature of 37°C, whereas 30°C was sufficient when detergent was used as well. The recovery of labile coagulation factors, especially FV and FVIII, was reduced at the higher temperature. Thus, Piet et al. recommend treatment with both solvent and detergent for the recovery of labile coagulation factors (i.e., coagulation factor zymogens), because solvent alone requires the use of higher temperatures which can denature labile proteins. It would not be possible to activate denatured prothrombin to thrombin. Thus, Piet et al. would lead the skilled person to believe that treatment with solvent alone at a higher temperature was unsuitable since it would inevitably result in

prothrombin denaturing, while treatment with solvent/detergent is undesirable since it results in a reduction in the yield of PCC. Accordingly, the method of Piet et al. is of limited practical value for the fractionation of the prothrombin complex coagulation factors and would not be an obvious choice for a skilled person with regard to generation of thrombin.

The process disclosed in Anderle et al. involves the use of a detergent in combination with a solvent, wherein the solvent is a carboxylic acid ester. Anderle et al. indicates that, with this specific combination of a carboxylic acid ester and detergent, pathogens in a protein solution are effectively inactivated while the protein activity is substantially fully preserved (see paragraph [0014] of Anderle). In contrast to Anderle et al., the S/D inactivation step in the presently amended claims uses tri-n-butyl phosphate as a solvent, and not a carboxylic acid ester, as was used in Anderle et al.

Moreover, as mentioned above, Anderle et al. teaches away from the presently claimed method of inactivating virus with a conventional S/D treatment prior to activation of prothrombin to yield thrombin. In particular, Anderle teaches at paragraph [0005] that there is a serine protease group, which includes the prothrombin complex of coagulation factors, which are sensitive to, and at least partially deactivated by conventional S/D methods. For these proteins, Anderle recommends that detergent alone be used at high concentrations (i.e., without solvent such as tri-n-butyl phosphate). In contrast, the presently claimed methods are able to utilize a S/D treatment step prior to activation of prothrombin because the methods also include a column washing step, wherein the solvent and detergent reagents used to inactivate virus are removed prior to subsequent activation of prothrombin to thrombin.

Based on the combined teachings of Kraus et al. Piet et al. and Anderle et al., the skilled artisan would have had no reason to believe that thrombin could be prepared by the presently claimed methods, wherein thrombin is activated after solvent-detergent virus inactivation of a prothrombin-containing sample.

Unexpected Results

The methods of the presently claimed invention provide unexpected results in view of Kraus et al. Piet et al. and Anderle et al. Based on the teachings of Anderle et al., one of skill in the art would predict that treating a prothrombin preparation with a conventional S/D treatment prior to activation of the prothrombin to yield thrombin would produce a thrombin preparation

having a lower specific activity than that seen by Kraus et al., given that Anderle et al teaches that prothrombin is partially deactivated by such conventional S/D methods. On the contrary, the specific activity of the thrombin preparations generated by the presently claimed methods surpasses that of preparations generated using the method of Kraus et al. The Kraus reference discloses that a specific activity (purity) of approximately 800 to 1400 units per mg of protein can be directly obtained using the methods disclosed therein. See Kraus et al. at column 2, lines 61-67. In order to achieve a specific activity of more than 2000 units per mg of protein, Kraus et al. acknowledges that additional purification steps, such as cation exchange must be conducted. In contrast, the Examples disclosed in the present specification describe the production of a product having greater than at least 2000 units per mg of protein without the need for cation exchange chromatography or other purification steps, which can diminish yield. Claims 1, 3, 16 and 21 are amended to specifically recite that a fraction of the thrombin has a specific activity of at least 2000 International Units per mg of protein.

Moreover, the presently claimed invention provides a high concentration of thrombin, which is surprisingly better than that achieved by Kraus et al. Kraus et al. does not directly specify the concentration of the thrombin obtained in the process disclosed therein. However column 2, line 58 of Kraus et al. indicates that the concentration can be increased to more than 100 units per mL by known methods, e.g., ultrafiltration. Thus, the concentration that is directly obtained from the methods described by Kraus et al. are necessarily lower than 100 units per mL. Such concentration methods are used in the pharmaceutical industry, but are cumbersome, expensive and time-consuming. Such a step would eliminate the benefits claimed in Kraus et al. of single step processing from plasma or plasma fraction. In contrast to the relatively low concentrations obtained by Kraus et al., as discussed in the Applicants previous response, the presently claimed invention provides a high thrombin concentration of more than 900 units per mL without the need for further processing steps.

In conclusion, the presently claimed methods provide a novel means to prepare thrombin from prothrombin, after pre-treatment of prothrombin with detergent to inactivate virus. The process yields both an unexpectedly high purity (Specific Activity > 2000 IU per mg of protein) and unexpectedly high concentration of thrombin. In contrast, extra steps are needed to produce thrombin by the method of Kraus et al. to achieve the same purity and potency as that obtained

using the process of the presently claimed invention incur a yield penalty, which would eliminate any upstream yield benefit. The necessary extra steps undermine the notion that the process of Kraus et al. has overcome the problem of multiple step processes for the preparation of thrombin. As discussed above, Piet et al. does not address whether thrombin can be activated from prothrombin after solvent-detergent virus inactivation of a sample containing prothrombin.

Based on the foregoing remarks, the claimed methods of the present application provide unexpected advantages over Kraus et al. in view of Piet et al. and Anderlie et al. Even had a proper *prima facie* showing of obviousness been set forth by the references cited, the unexpected results of high specific activity and high concentration of thrombin prepared by the presently claimed invention rebut any such showing.

Kraus et al. in view of Piet et al., Anderle et al., Kingdom et al. and Heimburger et al.

Claims 7, 15, 20 and 25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kraus et al. (*supra*) in view of Piet et al. (*supra*), Anderle et al. (*supra*), Kingdom et al. (U.S. Patent No. 5,354,682) and Heimburger et al. (U.S. Patent No. 6,346,277). However, since Claims 7, 15, 20 and 25 are ultimately dependent on Claims 1, 3, 16 and 21, respectively, they are not obvious in light of the remarks above. The disclosures of Kingdom et al. and Heimburger et al. do not provide additional information beyond the disclosures of Kraus et al. Piet et al. and Anderle et al. that would make the claimed methods obvious. Accordingly, the Applicants respectfully request removal of the rejections under 35 U.S.C. § 103(a).

<u>*No Disclaimers or Disavowals*</u>

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not

reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

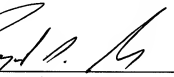
In view of Applicants' amendments to the Claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: November 20, 2009

By: 

Raymond D. Smith
Registration No. 55,634
Agent of Record
Customer No. 20995
(949) 760-0404

8138521
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